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TOWNSEND and TOWNSEND and CREW LLP

By: Jude Cotton

PATENT
Attorney Docket No. 020681-001710US

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| In re application of: | Confirmation No. 7974 |
| Hans E.J. Hofland | Examiner: Kishore, Gollamudi S. |
| Application No.: 10/713,546 | Technology Center/Art Unit: 1615 |
| Filed: November 14, 2003 | APPELLANTS' BRIEF UNDER 37 CFR §41.37 |
| For: LIPOSOMAL L-CARNITINE | |

Mail Stop Appeal Brief
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Further to the Notice of Appeal mailed on February 15, 2008 for the above-referenced application, Appellant submits this Brief on Appeal.

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**1. REAL PARTY IN INTEREST**

The real party in interest is Optime Therapeutics, Inc., the assignee of record.

**2. RELATED APPEALS AND INTERFERENCES**

No other appeals or interferences are pending in related Applications.

**3. STATUS OF CLAIMS**

Claims 1-11 were originally presented in the application. Claims 1-7 have been canceled without prejudice. Claims 8-11 have been rejected and are the subject of this appeal. No other claims are pending.

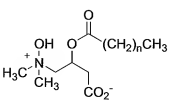
**4. STATUS OF AMENDMENTS**

No amendments have been submitted in response to the final office action dated August 16, 2007.

**5. SUMMARY OF CLAIMED SUBJECT MATTER**

The present invention relates to novel liposomal pharmaceutical compositions of L-carnitine derivatives and methods of using these compositions for treating peripheral arterial disease. The present invention is based on the surprising discovery that L-carnitine derivatives alone are effective in treating peripheral arterial disease when administered in liposomal formulations.

More particularly, independent claim 8 is directed to a method of treating a peripheral arterial disease in a mammal comprising administering a therapeutically effective amount of a liposomal formulation of an L-carnitine derivative, wherein the L-carnitine derivative is an alkyl-L-carnitine of formula



where n is an integer selected from the group consisting of 0, 4, 6, 8, 10, 12, 14, and 16 (Specification, page 2, lines 26-34; page 3, lines 7-10; page 5, lines 1-7).

Dependent claim 9 sets forth the feature that the mammal to be treated is a human. Dependent claim 10 sets forth the feature that the disease to be treated is intermittent claudication (Specification, page 1, line 7; page 2, lines 21-23).

Dependent claim 11 further identifies the L-carnatine derivative as either propionyl L-carnatine or acetyl L-carnatine (Specification, page 5, lines 4-7).

## 6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

A. Whether claims 8-11 are obvious under 35 U.S.C. §103(a) over U.S. Pat. No. 5,747,536 to Cavazza in view of U.S. Pat. No. 6,726,924 to Keller or U.S. Pat. No. 5,993,851 to Foldvari individually or in combination.

B. Whether claims 8-11 are obvious under 35 U.S.C. §103(a) over Brevetti (U.S. Pat. No. 4,968,719) in view of Keller (U.S. Pat. No. 6,726,924) or Foldvari (U.S. Pat. No. 5,993,851 ), individually or in combination, and further in view of Cavazza (U.S. Pat. No. 5,747,536).

## 7. ARGUMENT

A. Rejection under 35 U.S.C. §103(a) over Cavazza (U.S. Pat. No. 5,747,536) in view of Keller (U.S. Pat. No. 6,726,924) or Foldvari (U.S. Pat. No. 5,993,851 ) individually or in combination.

In the Office Action dated August 16, 2007, claims 1-11 were rejected under 35 U.S.C. §103(a), as allegedly being obvious over U.S. Pat. No. 5,747,536 to Cavazza, alone or in combination with Keller and Foldvari. In this regard, the Examiner alleges that Cavazza discloses L-carnitine and L-carnitine derivatives for the treatment of peripheral vascular diseases and further alleges that Keller discloses that the bioavailability of L-carnitine is increased when administered in a liposomal formulation. Moreover, the Examiner further cites Foldvari for allegedly teaching that liposomal encapsulation of biologically active agents alters the pharmacokinetic fate of the active agent. Therefore, the Examiner is of the opinion that the

invention is obvious over these references, alone or combined. Appellant respectfully traverses the rejection.

***NO PRIMA FACIE CASE OF OBVIOUSNESS EXISTS***

Appellant respectfully points out that the claims are drawn to a method of using certain alkyl-L-carnitine derivatives in a liposomal formulation for the treatment of peripheral arterial diseases, and asserts that a *prima facie* case of obviousness has not been established for the presently claimed invention.

As set forth in M.P.E.P. § 2141 (I), the Patent Office's policy is to follow *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966), in the consideration and determination of obviousness under 35 U.S.C. § 103. The four factual inquiries enunciated in *Graham* for determining obviousness are as follows:

(A) Determining the scope and contents of the prior art;

(B) Ascertaining the differences between the prior art and the claims in issue;

(C) Resolving the level of ordinary skill in the pertinent art; and

(D) Evaluating evidence of secondary considerations.

Recently, the U.S. Supreme Court affirmed the holding of *Graham* regarding obviousness. *See, KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727 (2007).

To establish a *prima facie* case of obviousness, 3 basic criteria must be met:

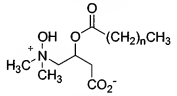
> First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Appellant respectfully submits that a *prima facie* case of obviousness has not been established because the cited references do not teach all the claimed limitations.

***The Cited References do not Teach or Suggest all the Claim Limitations.***

As discussed above, the claims are drawn to the use of a liposomal formulation comprising certain alkyl-L-carnitines as the active agent for treating peripheral arterial disease. Specifically, the claimed method, as set forth in claim 8, recites:

> Claim 8. A method for treating a peripheral arterial disease in a mammal, said method comprising:
>
> administering a therapeutically effective amount of a liposomal formulation of a L-carnitine derivative, wherein ***said L-carnitine derivative is an alkyl-L-carnitine of formula***



> ***wherein n is an integer selected from the group consisting of 0, 4, 6, 8, 10, 12, 14 and 16***, thereby treating a peripheral arterial disease in said mammal.

Appellant respectfully asserts that none of the cited references teach or suggest using an alkyl-L-carnitine, having the formula shown above, as the active agent in a liposomal formulation for treating peripheral arterial disease. In stark contrast to the present invention, the primary reference, Cavazza, is for the use of a pharmaceutical composition comprising a ***combination*** of L-carnitine (or derivatives thereof) ***and*** trihydroxy- or tetrahydroxy-stilbene (*see*, Title, Cavazza). Cavazza describes that the ***combination*** of active agents (*i.e.*, L-carnitine (or derivatives thereof) with trihydroxy- or tetrahydroxy-stilbene) exhibits synergistic pharmacologic effects to inhibit platelet aggregation and may be useful in treating cardiovascular diseases, peripheral vascular diseases, and diabetic peripheral neuropathy. In view of the teaching of Cavazza, Appellant respectfully asserts that a skilled artisan would not be motivated to modify Cavazza to arrive at the presently claimed invention as Cavazza simply does not suggest using alkyl-L-carnitines ***alone*** as the active agent in a pharmaceutical composition, much less in a liposomal formulation for the treatment of peripheral arterial disease as is presently claimed by Appellant.

A prior art reference must be considered in its entirety, ***i.e.,*** as a whole, including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983), cert. denied, 469, U.S. (1984).

Appellant respectfully asserts that Cavazza actually ***teaches away*** from the use of a pharmaceutical composition comprising alkyl-L-carnitine alone as the active agent for the treatment of peripheral arterial disease as presently claimed. Cavazza describes that the pathological basis of cardiovascular diseases, peripheral vascular diseases and diabetic peripheral neuropathy is undesired platelet aggregation. Cavazza performed ***in vitro*** platelet aggregation tests to quantify the inhibitory effects of, *inter alia*, L-carnitine alone, resveratrol alone (a trihydroxy-stilbene), and combination thereof on platelet aggregation and used these results to evaluate the potential effectiveness of these compounds for treating various disease, including cardiovascular diseases, peripheral vascular diseases, and diabetic peripheral neuropathy. In short, Cavazza discloses that L-carnitine, when used by itself, was ***completely ineffective*** at inhibiting platelet aggregation (***see***, col. 4, lines 51-62 of U.S. Pat. No. 5,747,536 to Cavazza).

The disclosure of Cavazza would clearly suggest to a skilled artisan that a composition comprising L-carnitine alone ***is not*** effective at treating the aforementioned diseases since Cavazza clearly teaches that L-carnitine (or derivatives thereof) alone does not inhibit platelet aggregation. Specifically, Cavazza teaches at column 4, lines 51-62:

> [Platelet] [a]ggregation was measured in basal conditions and after 10 minutes of incubation with L-carnitine, resveratrol, grape extract, and combinations of these preparations. ***Inhibition of the platelet aggregation induced by collagen (2.5 ng/ml) proved evident ($ED_{50}$ 3.5 ng/ml) for resveratrol and for grape extract ($ED_{50}$ with a resveratrol concentration equal to 2.5 ng/l), whereas for carnitine or its derivatives there was no significant change***. However, when using a combination of the carnitines plus resveratrol at the same doses, 100% inhibition of platelet aggregation was achieved, thus showing a marked synergism between L-carnitine and resveratrol or grape extract containing resveratrol. [Emphasis added.]

As stated above, Cavazza clearly discloses that L-carnitine (or derivatives thereof) alone ***would not*** be effective in treating peripheral vascular diseases such as peripheral arterial disease as is presently claimed by Appellant, and actually ***teaches away*** from this use alone.

Moreover, this deficiency of Cavazza is not supplemented by Keller or Foldvari. Keller describes an oral liposomal delivery system, which is a liposome-capsule dosage system, *i.e.* a "Lipocap." *See*, Abstract, Keller. Keller discloses preparing a lipocap formulation of L-carnitine, but does not teach or use L-carnitine derivatives, such as the presently claimed alkyl-L-carnitine derivatives, for treating peripheral arterial disease. Foldvari teaches the use of a liposomal formulation containing the active ingredient PGE1, or other related PGs, which act(s) by "*increasing arterial inflow through vasodila(tion)*", see column 3, lines 5-6 of the cited reference. Since, as disclosed in the specification of the instant application, "***it is not likely that vasodilators are effective*** (in treating intermittent claudication) *since the diseased vessels are usually the larger vessels that are already fully dilated*" Appellant respectfully asserts that Foldvari ***does not*** teach liposomal administration of active agents for the treatment of the type of peripheral arterial disease that is the focus of the instant application. As such, Foldvari also fails to address the deficiency of Cavazza.

In view of the above, Appellant respectfully submits that references do not teach or suggest all the claim limitations. Moreover, a skilled artisan, having possession of the cited references, would not be motivated to modify the references to arrive at the presently claimed invention as none of the cited references teach or suggest treating peripheral arterial disease using certain alkyl-L-carnitines as *the* active agent, much less a liposomal formulation of these alkyl-L-carnitines as is presently claimed by Appellant. In view of the foregoing, the withdrawal of the obviousness rejection by the Board is respectfully requested.

B. Rejection under 35 U.S.C. §103(a) over Brevetti (U.S. Pat. No. 4,968,719) in view of Keller (U.S. Pat. No. 6,726,924) or Foldvari (U.S. Pat. No. 5,993,851 ), individually or in combination, and further in view of Cavazza (U.S. Pat. No. 5,747,536).

In the Office Action dated August 16, 2007, claims 1-11 were rejected under 35 U.S.C. §103(a), as allegedly being obvious over U.S. Pat. No. 4,968,719 to Brevetti in view of U.S. Pat. No. 6,726,924 to Keller or U.S. Pat. No. 5,993,851 to Foldvari, individually or in combination, and further in view of Cavazza (U.S. Pat. No. 5,747,536). In this regard, the Examiner alleges that Brevetti teaches L-carnitine's effectiveness for the treatment of peripheral

vascular diseases and further alleges that Keller discloses that liposomes are sustained release delivery vehicles for a variety of agents including L-carnitine. The Examiner further cites Foldvari for allegedly teaching that liposomes (containing active agent PGE1) can be used to treat diseases including peripheral vascular disease. Finally, the Examiner alleges that Cavazza teaches the effectiveness of L-carnitine and its esters in the treatment of peripheral vascular diseases. Therefore, the Examiner is of the opinion that the invention of the instant application is obvious over the combination of the Brevetti reference with either or both of the Keller and Foldvari references and further with the Cavazza reference.

As outlined in the above argument, Appellant submits that that a skilled artisan, having possession of the Keller, Foldvari, and Cavazza references, would not be motivated to modify the references to arrive at the presently claimed invention as none of the cited references teach or suggest treating peripheral arterial disease using certain alkyl-L-carnitines as *the* active agent, much less a liposomal formulation of these alkyl-L-carnitines as is presently claimed by Appellant. Furthermore, Appellant respectfully submits that Brevetti does not supplement the deficiencies of the above references. By the Examiners admission on page 5 of the Office Action dated August 16, 2007:

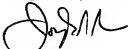
> Brevetti teaches L-carnitine's effectiveness for the treatment of peripheral vascular diseases (abstract, Examples and claims).What is lacking in Brevetti is the use of liposomes as the delivery vehicles for carnitine and the use of claimed derivatives of carnitine.

As such, the Brevetti reference does not supplement the deficiencies of the other cited references, namely the use of certain alkyl-L-carnitine derivatives as *the* active agent in treating peripheral arterial disease, much less a liposomal formulation of these alkyl-L-carnitines as is presently claimed by Appellant. In view of the foregoing, the withdrawal of the obviousness rejection by the Board is respectfully requested.

## 8. CONCLUSION

For these reasons, it is respectfully submitted that the rejections should be reversed.

Respectfully submitted,



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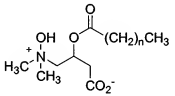
## 9. CLAIMS APPENDIX

**8.** (Previously Presented) A method for treating a peripheral arterial disease in a mammal, said method comprising:

administering a therapeutically effective amount of a liposomal formulation of a L-carnitine derivative, wherein said L-carnitine derivative is an alkyl-L-carnitine of formula



wherein n is an integer selected from the group consisting of 0, 4, 6, 8, 10, 12, 14 and 16, thereby treating a peripheral arterial disease in said mammal.

**9.** (Original) The method according to claim **8**, wherein said mammal is a human being.

**10.** (Original) The method according to claim **8**, wherein said disease or symptom is intermittent claudication.

**11.** (Previously Presented) The method according to claim **8**, wherein said L-carnitine derivative is selected from the group consisting of propionyl L-carnitine and acetyl L-carnitine.

**10. EVIDENCE APPENDIX**

None.

**11. RELATED PROCEEDINGS APPENDIX**

None.